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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/712,122	11/13/2003	John D. Pluenneke	3369-A	7679

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EXAMINER	
RAE, CHARLESWORTH E	
ART UNIT	**PAPER NUMBER**
1614	

DATE MAILED: 10/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/712,122	PLUENNEKE, JOHN D.	
	Examiner	Art Unit	
	Charleswort Rae	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *3-7* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2 and 8-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/1/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

The following is responsive to applicant's amendment and remarks received May 23, 2006. Claims 1-2 and 8-17 are pending and are the subject of this Office action. Claims 3-7 have been withdrawn.

Restriction/Election

Applicant's election with traverse of Group I (claims 1-2 and 8-17) and the ABX-EGF species in the reply on May 23, 2006, is acknowledged. The traversal is on the ground that it would not be unduly burdensome to search the claims. This is not found persuasive because applicant has only asserted a conclusory statement without pointing out any supposed errors in the restriction to support the conclusion.

The requirement is still deemed proper and is therefore made FINAL.

With respect to the election of the species ABX-EGF, this election requirement is being withdrawn for examination purposes. All species of EGFR inhibitor are under examination.

Claim Rejections – 35 USC 112 – First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2 and 8-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating EGFR+ cancers, including osteosarcomas, glioblastoma, gliomas, melanomas, and meningiomas, and lung,

breast, head and neck, bladder, ovarian, skin, prostate, cervical, gastric, renal cell, pancreatic, colorectal, endometrial, esophageal cancers (see Specification, page 10, lines 2-8), does not reasonably provide enablement for any and all cancers in which the "cancer cells express the CCKβ/gastrin receptor and express little or no EGFR." This is a scope enablement rejection.

Specifically, applicant discloses a "method for reducing tumor burden comprising administering to a patient suffering from a hematologic cancer therapeutically effective amounts of an EGFR inhibitor and an anti-neoplastic agent wherein the anti-neoplastic agent is not a farnestyltransferase inhibitor and wherein the hematologic cancer cells express little or no EGFR." (See specification, page 2 line 30 to page 3 line 3). Applicant also asserts that "EGFR inhibitors can prevent or delay the onset of colorectal cancer through direct effects on cell proliferation and through effects on the transcription of the gastrin gene and the phosphorylation of gastrin. (see specification, page 34, line 31 to page 35, line 2). However, applicant's definition of "EGFR inhibitors" includes "any molecule that can affect the biological activity of EGFR ..." (see specification, page 6, lines 15-20). To the extent that colorectal cancer and hematologic cancers may express EGFR, these cancers fall within the scope of EGFR+ cancers. It also follows that the subpopulation of patients with EGFR+ and CCKβ/gastrin receptor+ colorectal cancer do overlap, as well as the subpopulation of patients with EGFR+ and CCKβ/gastrin receptor+ hematologic cancer.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without

undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fd. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if its is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth in *In re Wands,* 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman* 230 USPQ 546 (BdApls 1986) at 547 the court cited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence or absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) the breadth of the claims

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping

that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art.

The invention in general relates to a method for reducing tumor burden in patients suffering from cancers in which the cancer cells express CCKβ/gastrin receptor and little or no EGFR. The relative skill of those in the art is high, generally that of an M.D. or Ph.D. That factor is outweighed, however, by the unpredictable nature of the art. It is noted that the pharmaceutical art is generally unpredictable, requiring each embodiment to be individually assessed for physiological activity. The more unpredictable an area, the more specific enablement is necessary in order to satisfy the statue. (see *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970)). For example, the mode of action of anticancer drugs is often unknown or very unpredictable and administration of such agents is often accompanied by undersirable effects. Although cancer cells proliferate rapidly, the rate of growth varies widely depending on the particular cancer cell type. This variability in the rate of growth may also affect the therapeutic responsiveness of cancer cells. Besides, there is a disproportionately sparse number of discovery of new and predictable curative cancer treatments compared with the vast number of new drugs discovered.

The unpredictability or uncertainty in the art is illustrated by the fact that applicant asserts that "[a]lthough the identity of the gastrin receptor that mediates the growth-promoting effects of gastrin in tumors is not certain, the CCKβ/gastrin receptor is a

characterized gastrin receptor that may play this role." (see specification, page 35, lines 12-20). Further, applicant discloses that gastrin can promote the synthesis and processing of hb-EGF, ..., and the tyrosine phosphorylation of EGFR in a rat gastric epithelial cell line." (see specification, page 35, lines 27-29). Arguably, if gastrin is capable of promoting the synthesis and processing of EGF, then cancer cells that express CCKβ/gastrin receptors would more likely than not also express EGF. Thus, one skilled in the art would not be able to extrapolate the disclosed teachings of the claimed invention to cancer types that express CCKβ/gastrin receptor and little or no EGFR.

2. The breadth of the claims

The claims vary in breadth; some (such as claims 1 and 12) vary broadly, reciting the method for "reducing tumor burden" of cancers that express the "CCK " and express" little or no EGFR." Others, such as claims 2 and 8, are narrower, reciting EGFR small molecule inhibitor and EGFR protein inhibitor. All, however, are extremely broad insofar as they disclose a method of reducing tumor burden in patients suffering from multiple types of cancers that express CCK β/gastrin receptor and little or no EGFR. Because the therapeutic response to be achieved would necessarily vary depending upon the type of cancer being treated and the specific EGFR inhibitor used, the level of predictably in practicing the claimed invention would be greatly diminished.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for determining the

particular administration regimens (dosages, timing, administration routes etc.) necessary to treat all cancers that "express the CCKβ/gastrin receptor and express little or no EGFR". The 'working examples" are limited to example administration regimens for the treatment of cancers that express EGFR. Thus, the applicant at best has provided specific direction or guidance only for a general administration protocol for treatment of EGFR+ tumors. No reasonably specific guidance is provided concerning useful therapeutic protocols or specific agents for treating cancers that "express the CCKβ/gastrin receptor and express little or no EGFR".

4. The quantity of experimentation necessary

In view of applicant's disclosure that "transcription factors regulated by EGF and TGFα can promote transcription of gastrin, an effect that may or may not be mediated by EGFR ..." (see specification, page 34, lines 25-30), it is reasonable to surmise that this level of uncertainty in the art would require one skilled in the art to conduct more than routine experimentation in order to practice the claimed invention in cancer patients wherein the cancer cells express CCKβ/gastrin receptor and express little or no EGFR. Thus, based on the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the instantly claimed methods could be predictably used as treatments for any cancer wherein the "cancer cells express the CCKβ/gastrin receptor and little or no EGFR."

For the reasons stated above, claims 1-2 and 8-17 are rejected under 35 USC 112, first paragraph, for lack of scope enablement because the specification does not

enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with the claims.

Claim rejections – 35 USC 112 – Second Paragraph

The following is a quotation of the second paragraph of 35 USC 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

First, claim 1-2 and 8-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the term "therapeutically effective amount," but fails to state the function which is to be achieved even though more than one effect can be implied from the specification. Is it a "therapeutically effective amount" to reduce tumor burden? Or, is it a "therapeutically effective amount" to reduce something other than tumor burden, for example, cancer pain? This limitation is indefinite because it is not clear what "therapeutically effective amount" means.

It is note that the preamble of claim 1 recites the term "[a] method for reducing tumor burden." However, the term "[a] method for reducing tumor burden" is not clearly connected to the term "therapeutically effective amount." It is therefore suggested that applicant amend claim 1 in a manner that clearly and concisely connect the preamble with the body of the claim e.g. amend claim 1 to read "therapeutically effective amount to reduce tumor burden" provided support is found in the specification as originally filed.

Claims dependent from claim 1 (i.e. claims 2, and 8-17) are also rejected under 35 USC 112, 2nd paragraph for the same reason stated because the limitations recited in the dependent claims fail to overcome the deficiency of claim 1.

Second, claims 1-2 and 8-17 are also rejected under 112, second paragraph, on separate grounds for being indefinite for omitting matter disclosed to be essential to the invention as described in the specification.

Claim 1 recites the term "cancer cells express the CCKβ/gastrin receptor and express little or no EGFR." Clearly, the instant claimed invention requires that the cancer cells of the patient suffering from cancer express CCKβ/gastrin receptor and express little or no EGFR, nothwitstanding the fact that gastrin could promote the synthesis of EGF. (see specification, page 35, lines 27-29). Claim 1 therefore fails to recite an essential step requiring the determination of the expression of CCKβ/gastrin receptor and "little or no EGFR" by cancer cells prior to administering the EGFR inhibitor. Thus, claimed 1 is indefinite for omitting matter disclosed to be essential to the claimed invention.

Claims dependent from claim 1 (i.e. claims 2, and 8-17) are also rejected under 35 USC 112, 2nd paragraph for the same reason stated because the limitations recited in the dependent claims fail to overcome the deficiency of claim 1.

It is suggested that this rejection may be overcome by amending claim 1 to recite a additional step prior to administering the EGFR inhibitor pharmaceutical composition to a patient, for example, "determining the expression of EGFR and CCKβ/gastrin

receptor by the cancer cells" provided there is support in the specification for the amendment.

Third, claims 1-2 and 8-17 are further rejected under 112, second paragraph for being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "little or no EGFR." The term "little or no EGFR" is unclear. "Little" compared to what? To the extent that EGFR expression is measured in nanomolar amounts, "little EGFR" could actually mean a lot. Further, "little or no EGFR" could also be interpreted as being equivalent to an "infinitesimal" or "undectable" amount of EGFR. It is suggested that applicant amend the claim to correct this ambiguity.

Claim rejections – 35 USC 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 8-10, and 15-16 are rejected under 35 USC 102(b) as being anticipated by Yang *et al.* (Critical Reviews in Oncology/Hematology, 2001, vol. 38, pages 17-23)

Yang *et al.* teach ABX-EGF for treating EGFR+ cancers. (Yang et al., page 17).

Yang *et al.* teach away from using ABX-EGF for treating EGFR- cancers (Yang et al., page 17).

Claim 1 recites "administering a therapeutically effective amount of an EGFR inhibitor, for example, ABX-EGF, to a human patient suffering from a cancer." As stated above, Yang *et al.* also teach administering an EGFR inhibitor, ABX-EGF, to a patient suffering from an EGFR+ cancer.

Claim 1 also recites the limitation that the "cancer cells express the CCKβ/gastrin receptors and/or no EGFR." Yang *et al.* does not expressly teach that the "cancer cells express the CCKβ/gastrin receptors and/or no EGFR," this teaching is inherent as applicant's stated definition of EGFR inhibitors ("... any molecule that can affect the biological activity of EGFR," see specification, page 6, lines 15-20), necessarily requires that the EGFR inhibitors encompassed by the instant claimed invention possess the property of reducing tumor burden of patients suffering from a cancer in which the cancer cells express the CCKβ/gastrin receptor and little or no EGFR.

Further, applicant discloses a "method for reducing tumor burden comprising administering to a patient suffering from a hematologic cancer therapeutically effective amounts of an EGFR inhibitor and an anti-neoplastic agent wherein the anti-neoplastic agent is not a farnestyltransferase inhibitor and wherein the hematologic cancer cells express little or no EGFR." (See specification, page 2 line 30 to page 3 line 3). Applicant also asserts that "EGFR inhibitors can prevent or delay the onset of colorectal cancer through direct effects on cell proliferation and through effects on the transcription of the

gastrin gene and the phosphorylation of gastrin. (see specification, page 34, line 31 to page 35, line 2). To the extent that colorectal cancer and hematologic cancers fall within the scope of EGFR+ cancers, coupled with the fact that there is a clear overlap of patients with colorectal cancer and hematologic cancer that expresss EGFR and/or CCKβ/gastrin receptors, claim 1 is anticipated in view of the teaching of Yang *et al.*

Claims 8 recites the limitation "the EGFR inhibitor is a protein." ABX-EGF is a protein as it is a fully human anti-EGF receptor monoclonal antibody. Thus, claim 8 is anticipated in view of the teaching of Yang *et al.*

Claims 9-10, and 15 -16, recite the limitation "an inhibitor of the interaction between gastrin and the CCKβ/gastrin receptor." Applicant defines "an inhibitor of the interaction between gastrin and CCKβ/gastrin receptor" to include " ... proteins, nucleic acids (such as antisense molecules, ribozymes, DNA enzymes, triple helix-forming nucleic acids, or interfering RNAs), or small molecules that interfere with the expression of gastrin or the CCKβ/gastrin receptor ..." (see specification, page 37, line 30 to page 38, line 1). Applicant also discloses that "transcription factors regulated by EGF and TGFα can promote transcription of gastrin, an effect that may or may not be mediated by EGFR ..." (see specification, page 34, lines 25-30). Thus, claims 9-10 and 15-16, encompass EGFR inhibitors, including ABX-EGF, which may directly or indirectly interfere with the expression of gastrin or the CCKβ/gastrin receptor. In view of the teaching of Yang *et al.*, these claims are also anticipated.

Claims 2, 11-14 and 17 are rejected under 102(b) as being anticipated by Noonberg *et al.* (Drugs, 2000, vol. 59, no. 4, pages 753-767).

Noonberg *et al.* teach EGFR small molecule inhibitors and EGFR protein inhibitors for treating EGFR+ cancers, including leukemia and lymphomas. (Drugs, 2000, vol. 59, no. 4, pages 754-763).

Noonberg *et al.* does not expressly teach using EGFR protein inhibitors and EGFR small molecule inhibitors for treating cancer patients suffering with cancer cells that express CCKβ/gastrin receptors and/or no EGFR.

Claim 2 recites the limitation "wherein the EGFR inhibitor is a small molecule." As stated above, Noonberg *et al.* also teach administering an EGFR small molecule inhibitor to a cancer patient with EGFR+ cancer. Although Noonberg *et al* does not expressly teach that the "cancer cells express the CCKβ/gastrin receptors and/or no EGFR," this teaching is inherent as applicant's stated definition of EGFR inhibitors "including any molecule that can affect the biological activity of EGFR," (see specification, page 6, lines 15-20), necessarily requires that the EGFR inhibitors encompassed by the instant claimed invention possess the property of reducing tumor burden of patients suffering from a cancer in which the cancer cells express the CCKβ/gastrin receptor and little or no EGFR. Thus, claim 2 is anticipated in view of the teaching of Noonberg *et al.*

Claim 11 recites the limitation "wherein interaction between gastrin and the CCKβ/gastrin receptor is a small molecule." As discussed above, applicant's definition of "an inhibitor of the interaction between gastrin and CCKβ/gastrin receptor" includes EGFR small molecule inhibitors (see specification, page 37, line 30 to page 38, line 1).

To the extent that EGFR small molecule inhibitors may directly or indirectly interfere with the expression of gastrin or the CCKβ/gastrin receptor, claim 11 is anticipated in view of the teaching of Noonberg *et al.*

Claims 12, 13, 14 and 17 also recite the limitation "administering an inhibitor of the interaction between gastrin and the CCKβ/gastrin receptor," which may be a small molecule or protein. For the reasons stated above, these claims are also anticipated in view of the teaching of Noonberg *et al.*

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charlesworth Rae whose telephone number is 571-272-6029. The examiner can normally be reached between 8 a.m. to 4:30 p.m. Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached at 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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6 October 2006
CER

Ardin H. Marschel 10/14/06
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